Methods

Data analysis

A full Bayesian evidence network was used in the network meta-analysis (chains: 4; initial values scaling: 2.5; tuning iterations: 20.000; simulation iterations: 50.000; tuning interval: 10). The convergence diagnostics for consistency and inconsistency were assessed via the Brooks-Gelman-Rubin method, as previously described [1]. Results of the network meta-analysis are expressed as relative effect (RE) and 95% credible interval (95%CrI). The probability that each intervention arm was the most effective was calculated by counting the proportion of iterations of the chain in which each intervention arm had the highest mean difference, and the surface under the cumulative ranking curve (SUCRA), representing the summary of these probabilities, was also calculated [2]. The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [3].

Quality score and risk of bias

The Jadad score, with a scale of 1 to 5 (score of 5 being the best quality), was used to assess the quality of the RCTs concerning the likelihood of biases related to randomization, double blinding, withdrawals and dropouts [4]. A Jadad score ≥3 was defined to identify high-quality studies. Two reviewers (MC and LC) independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of publication bias in the pairwise meta-analysis was assessed for primary endpoints by applying the funnel plot and Egger's test, as previously described [4]. Evidence of asymmetry from Egger's test was considered to be significant at $P<0.1$, and the graphical representation of 90% confidence bands were presented [4]. The risk of bias in the network meta-analysis was assessed via the consistency/inconsistency analysis to check whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [5]. Furthermore, the inconsistency of evidence was also assessed by quantifying the

inconsistency factor, indicating whether one of the treatment had a different effect when it was compared with the others [6].

Results

The risk of SAEs was not significantly (P>0.05) different between ICS/LABA/LAMA combination and LABA/LAMA combination (RR 0.96, 95%CI 0.88 – 1.04, I^2 0%), whereas a significantly (P<0.05) lower risk of SAEs was detected when comparing ICS/LABA/LAMA combination with single long-acting bronchodilator therapy (RR 0.84, 95%CI 0.73 – 0.98, I^2 0%).

Since the change from baseline in trough FEV_1 was a continuous outcomes, we have dichotomized this variable [7] by using the responder analysis. Specifically, we considered responder patients those that had ≥100 ml increase from baseline in trough FEV_1, as previously indicated [8, 9]. Among the studies included in this meta-analysis, only the TRIBUTE and TRINITY RCTs [10, 11] preformed the responder analyses for FEV_1. Considering the change from baseline in trough FEV_1, the NNTs of ICS/LABA/LAMA combination vs. LABA/LAMA combination and single long-acting bronchodilator therapy were 36.85 (95%CI 21.38 – 144.76) and 9.56 (95%CI 7.33 – 13.87), respectively.

The levels of heterogeneity were confirmed by dispersion resulting from the visual analysis of funnel plots. Nevertheless, the Egger's test identified significant asymmetry only for the effect of ICS/LABA/LAMA combination on the risk of moderate or severe AECOPD (Figure S5A and B). The sensitivity analysis indicated that the IMPACT study [12] represented the main source of asymmetry: removing that study [12] from Egger's test reduced asymmetry at not significant levels (P>0.1) and decreased the efficacy of triple combination therapy in protecting against the risk of moderate or severe AECOPD (RR 0.90, 95%CI 0.83 – 0.97; P<0.05 vs. LABA/LAMA combination). Conversely, Egger's test did not identify any significant asymmetry with respect to the impact of ICS/LABA/LAMA combination on the change from baseline in FEV_1 and risk of pneumonia, indicating that no publication bias affected the effect

estimates of these primary endpoints (Figure S5C-F). The inconsistency factor resulting from the network meta-analysis was not significant (P>0.05), and the overall consistency/inconsistency analysis indicated that all points fit adequately with the line of equality (efficacy: R^2 0.99, slope 1.00 and 95%CI 0.997 – 1.003).

The GRADE analysis indicated moderate quality of evidence (+++) for the impact of ICS/LABA/LAMA combination vs. LABA/LAMA combination on the risk of moderate or severe AECOPD. High quality of evidence (++++) was detected for the impact of ICS/LABA/LAMA combination vs. single long-acting bronchodilator therapy on the risk of moderate or severe AECOPD, and for ICS/LABA/LAMA combination vs. LABA/LAMA combination and single long-acting bronchodilator therapy with regard to the change from baseline in FEV_1 and the risk of pneumonia (Table S3).

Supplementary tables

Table S1. PRISMA-P 2015 Checklist [13].

Section and topic	Item n	Checklist item	Reported on page of submitted manuscript
		Administrative information	
Title:			
Identification	1a	Identify the report as a protocol of a systematic review or meta-analysis	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
		Introduction	
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
		Methods	
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3, 4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	3, 4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	3, 4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	3, 4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6, 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	4, 5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	4, 5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)		Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	4, 5
Confidence in cumulative evidence		Describe how the strength of the body of evidence will be assessed (such as GRADE)	4, 5

NA: not applicable; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

Table S2. COPD patient demographics, baseline and study characteristics.

Study, year, clinical trial identifier, reference	Trial characteristics	Duration of treatment (weeks)	Number of analyzed patients	Drugs, doses, regimen of administration, device	Main inclusion criteria	Age (years)	Male (%)	Current smokers (%)	Smoking history (pack-years)	Post bronchodilator FEV_1 (% predicted)	Patient with AECOPD history (%)	AECOPD in the previous year (rate)	Blood eosinophils subgroups (cells per µL)	Jadad score
SUNSET, 2019, NCT02603393 [14]	Randomized, triple-blind, parallel-group, active control, multicenter.	26	1,053	FP/SAL+TIO (500/50 µg, BID, via MDI + 18 µg, OD, via DPI HandiHaler); GLY/IND (50/110 µg, OD, via DPI Breezhaler).	FEV_1 ≥40% and <80% predicted and ≤1 moderate severe AECOPD in the previous year.	65	70	NA	≥10	57%	34	NA	<300; ≥300	5
IMPACT, 2018, NCT02164513 [12]	Phase III, randomized, double-blind, parallel-group, active control, multicenter.	52	6,221	FF/UMEC/VI (100/62.5/25 µg, OD, via DPI Ellipta); UMEC/VI (62.5/25 µg, OD, via DPI Ellipta).	a) FEV_1 <50% predicted and ≥1 moderate or severe AECOPD in the previous year; b) FEV_1 ≥50% and ≤80% predicted and ≥2 moderate or ≥1 severe AECOPD in the previous year.	65	67	35	≥10	45%	100	1.7	<150; ≥150	3
TRIBUTE, 2018, NCT02579850 [11]	Phase IIIb, randomized, double-blind, double-dummy, parallel-group, active control, multicenter.	52	1,532	BDP/FOR/GLY (100/6/12.5 µg, BID, via pMDI); GLY/IND (43/85 µg, OD, via DPI Breezhaler).	FEV_1 <50% predicted and ≥1 moderate or severe AECOPD in the previous year.	64	72	45	≥10	<50% (1.07L)	100	1.2	<200; ≥200	5
TRINITY, 2017, NCT019113 64 [10]	Randomized, double-blind, double-dummy, parallel-group, active control, multicenter.	52	2,691	BDP/FOR/GLY (100/6/12.5 µg, BID, via pMDI); BDP/FOR+TIO (100/6 µg, BID, via pMDI + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 <50% predicted and ≥1 moderate or severe AECOPD in the previous year.	63	77	48	≥10	36%	100	1.3	<200; ≥200	5
Lee, 2016, NCT01397890 [15]	Randomized, open-label, parallel-group, active control, multicenter.	12	578	BUD/FOR+TIO (320/9 µg, BID, via DPI Turbuhaler + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 <65% and ≥1 AECOPD requiring a course of oral steroids and/or antibiotics within 1–12 months	67	96	NA	≥10	36%	100	NA	NA	2
Saito, 2015 [16]	Randomized, double-blind, double-dummy, crossover, active control, multicenter.	4	50	FP/SAL+TIO (250/50 µg, BID, via DPI Diskus + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 ≥30% to ≤75%.	67	98	36	46	59%	0	0	NA	4
WISDOM, 2014, NCT00975195 [17]	Randomized, double-blind, parallel-group, active control, multicenter.	52	2.485	FP/SAL+TIO (500/50 µg, BID, via MDI + 18 µg, OD, via DPI HandiHaler); SAL+TIO (50 µg, BID, via pMDI + 18 µg, OD, via DPI HandiHaler).	FEV_1 <50% and ≥1 AECOPD in the previous year.	64	83	33	≥10	34%	100	NA	<150; ≥150; ≥300; ≥400	4
Hoshino, 2013 [18]	Randomized, open-label, parallel-group, active control, single center.	16	44	FP/SAL+TIO (250/50 µg, BID, via DPI Diskus + 18 µg, OD, via DPI HandiHaler); SAL (50 µg, BID, via pMDI); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 <70%	73	90	NA	55	<70% (1.40L)	NA	NA	NA	3
Jung, 2012 [19]	Randomized, open-label, parallel-group, active control, multicenter.	24	479	FP/SAL+TIO (250/50 µg, BID, via DPI Diskus + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 <65%	67	98	NA	≥10	47%	NA	NA	NA	3

Hanania, 2012, NCT00784550 [20]	Randomized, double-blind, parallel-group, active control, multicenter.	24	342	FP/SAL+TIO (250/50 µg, BID, via DPI Diskus + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 ≥40% to ≤80%.	61	47	58	55	57%	34	0.42	NA	4
CLIMB, 2009, NCT00496470 [21]	Randomized, double-blind, parallel-group, active control, multicenter.	12	660	BUD/FOR+TIO (320/9 µg, BID, via DPI Turbuhaler + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 ≤50% and ≥1 AECOPD requiring systemic steroids and/or antibiotics, in the previous year.	62	75	44	37	38%	100	1.4	NA	4
Singh, 2008, NCT00325169 [22]	Randomized, double-blind, double dummy, crossover, active control, multicenter.	2	31	FP/SAL+TIO (500/50 µg, BID, via DPI Diskus + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 >30% to ≤75%.	63	77	47	46	47%	40	0.4	NA	4
Cazzola, 2007 [23]	Pilot, randomized, double-blind, double-dummy, parallel-group, active control, multicenter.	12	55	FP/SAL+TIO (500/50 µg, BID, via DPI Diskus + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 <50%	67	90	82	49	39%	NA	NA	NA	4
OPTIMAL, 2007, ISRCTN29870041 [24]	Randomized, double-blind, parallel-group, active control, multicenter.	52	449	FP/SAL+TIO (500/50 µg, BID, via pMDI + 18 µg, OD, via DPI HandiHaler); SAL+TIO (50 µg, BID, via pMDI + 18 µg, OD, via DPI HandiHaler); TIO (18 µg, OD, via DPI HandiHaler).	FEV_1 <65% and ≥1 AECOPD requiring systemic steroids or antibiotics in the previous year.	68	56	28	50	39%	100	NA	NA	5

AECOPD: acute exacerbation of COPD; BID: bis in die; BDP: beclometasone dipropionate; BUD: budesonide; DPI: dry-powder inhaler; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FOR: formoterol fumarate; FF: fluticasone furoate; FP: fluticasone propionate; GLY: glycopyrronium bromide; IND: indacaterol; MDI: metered-dose inhaler; NA: not available; OD: once daily; pMDI pressurised metered-dose inhaler; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium bromide; VI: vilanterol.

Table S3. GRADE evidence profile: impact of ICS/LABA/LAMA combination vs. LABA/LAMA combination and single long-acting bronchodilator therapy on the risk of moderate or severe AECOPD, change from baseline in FEV_1, and risk of pneumonia in COPD patients.

		Quality assessment					
Question	**Outcome**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality of evidence**
Should ICS/LABA/LAMA combination vs. LABA/LAMA combination be used in COPD patients?	**Risk of moderate or severe AECOPD**	Not serious	Serious[a]	Not serious	Serious[b]	All plausible residual confounding would suggest spurious effect, while no effect was observed.	⊕⊕⊕◯ MODERATE
Should ICS/LABA/LAMA combination vs. single long-acting bronchodilator therapy be used in COPD patients?		Not serious	Serious[a]	Not serious	Serious[b]	Strong association; all plausible residual confounding would suggest spurious effect, while no effect was observed.	⊕⊕⊕⊕ HIGH
Should ICS/LABA/LAMA combination vs. LABA/LAMA combination be used in COPD patients?	**Change from baseline in FEV_1**	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Should ICS/LABA/LAMA combination vs. single long-acting bronchodilator therapy be used in COPD patients?		Not serious	Serious[a]	Not serious	Not serious	Strong association; all plausible residual confounding would suggest spurious effect, while no effect was observed.	⊕⊕⊕⊕ HIGH
Should ICS/LABA/LAMA combination vs. LABA/LAMA combination not be used in COPD patients?	**Risk of pneumonia**	Not serious	Not serious	Not serious	Serious[c]	Strong association; all plausible residual confounding would suggest spurious effect, while no effect was observed.	⊕⊕⊕⊕ HIGH
Should ICS/LABA/LAMA combination vs. single long-acting bronchodilator therapy not be used in COPD patients?		Not serious	Not serious	Not serious	Serious[c]	Strong association	⊕⊕⊕⊕ HIGH

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

a. as confirmed by I^2
b. 95%CI included RR of 0.75
c. 95%CI overlapped the line of equality (RR of 1.0)
AECOPD: acute exacerbation of COPD; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic receptor antagonist.

Supplementary figures

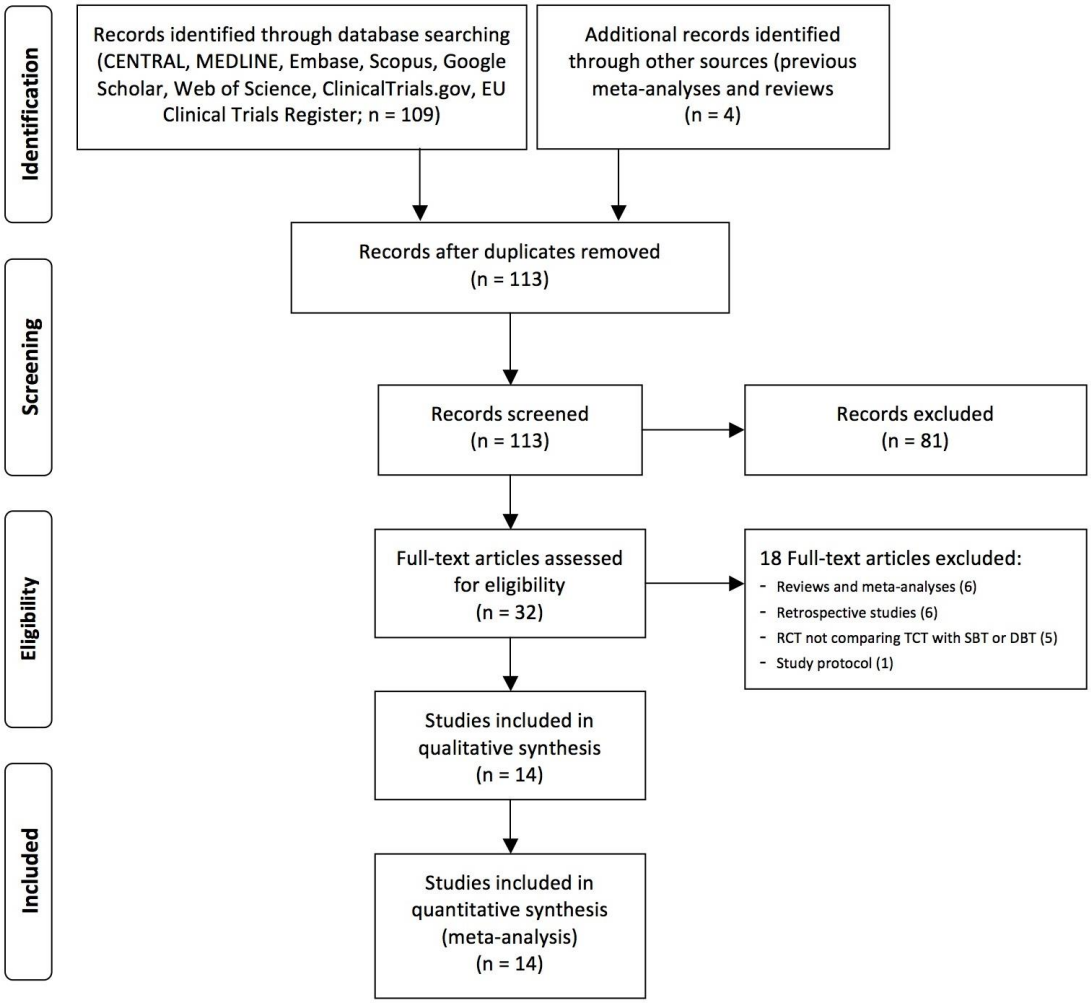

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) flow diagram for the identification of studies included in the meta-analysis concerning the impact of triple combination therapy vs. single and dual bronchodilator therapy in chronic obstructive pulmonary disease (COPD).

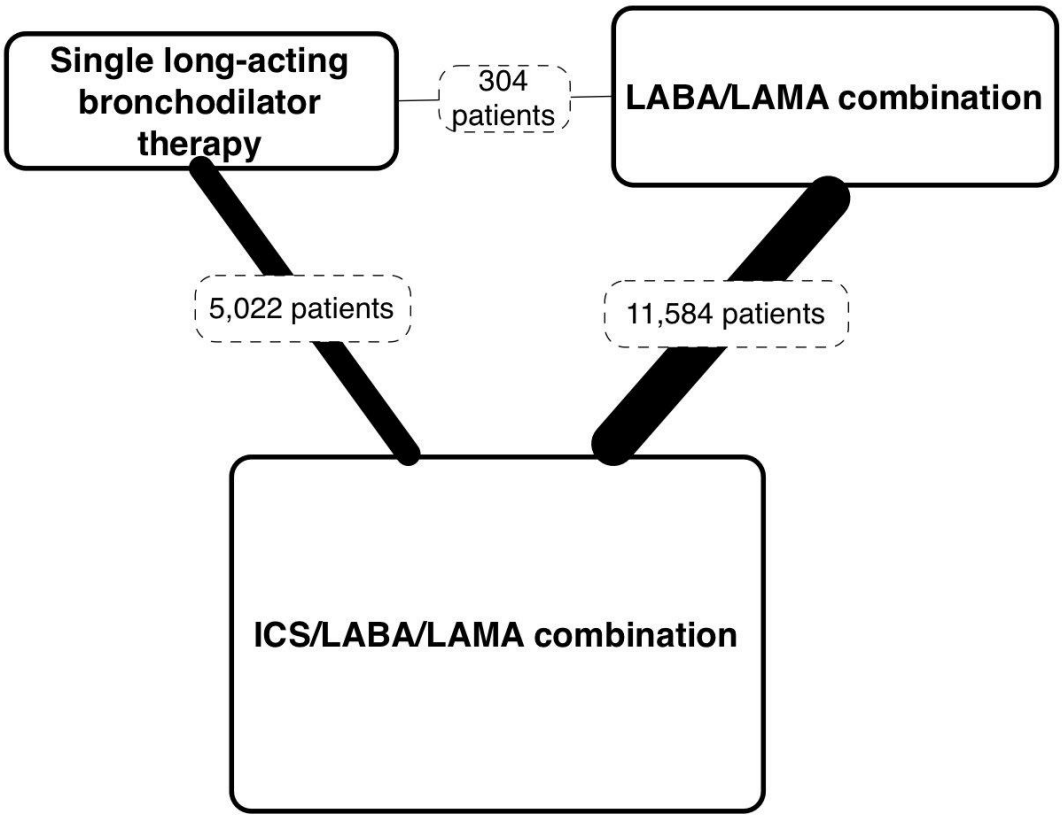

Figure S2. Diagram displaying the network of the arms involved in the Bayesian analysis. The links between nodes indicate the direct comparisons between pairs of treatments. The numbers shown along the link lines indicate the number of COPD patients comparing pairs of treatments head-to-head. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic receptor antagonist.

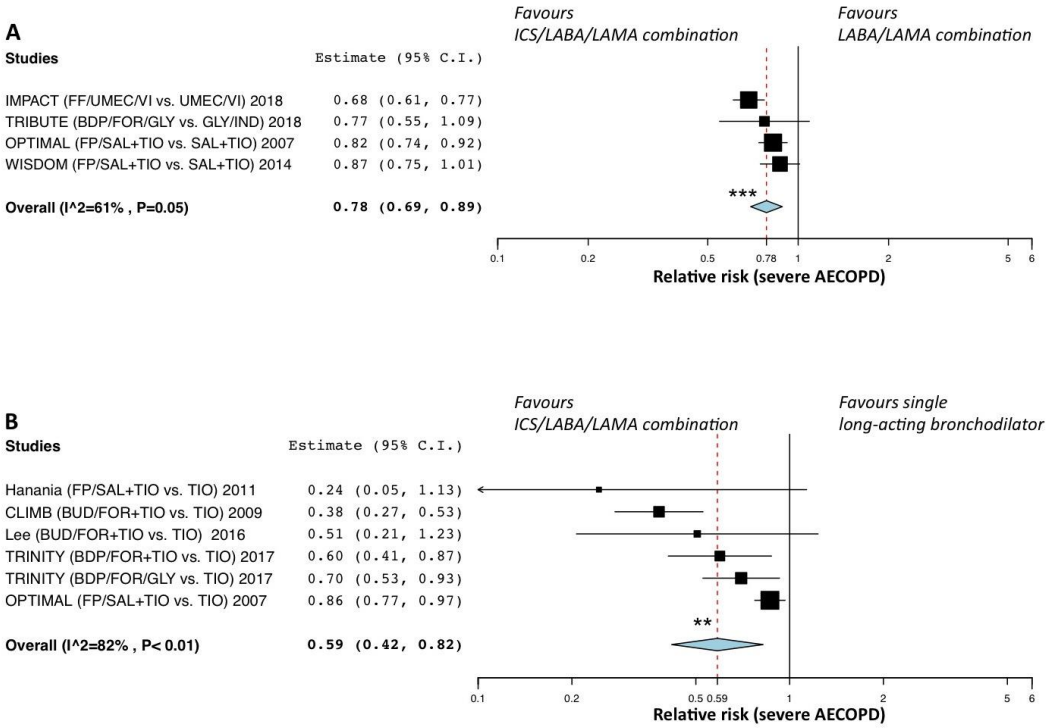

Figure S3. Forest plot of the impact of ICS/LABA/LAMA combination vs. LABA/LAMA combination (A) and single long-acting bronchodilator therapy (B) on the risk of severe AECOPD in COPD patients. The studies have been sorted by the extent of effect. **P<0.01 and ***P<0.001 vs comparators. AECOPD: acute exacerbation of COPD; BDP: beclometasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FOR: formoterol fumarate; FF: fluticasone furoate; FP: fluticasone propionate; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic receptor antagonist; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium bromide; VI: vilanterol.

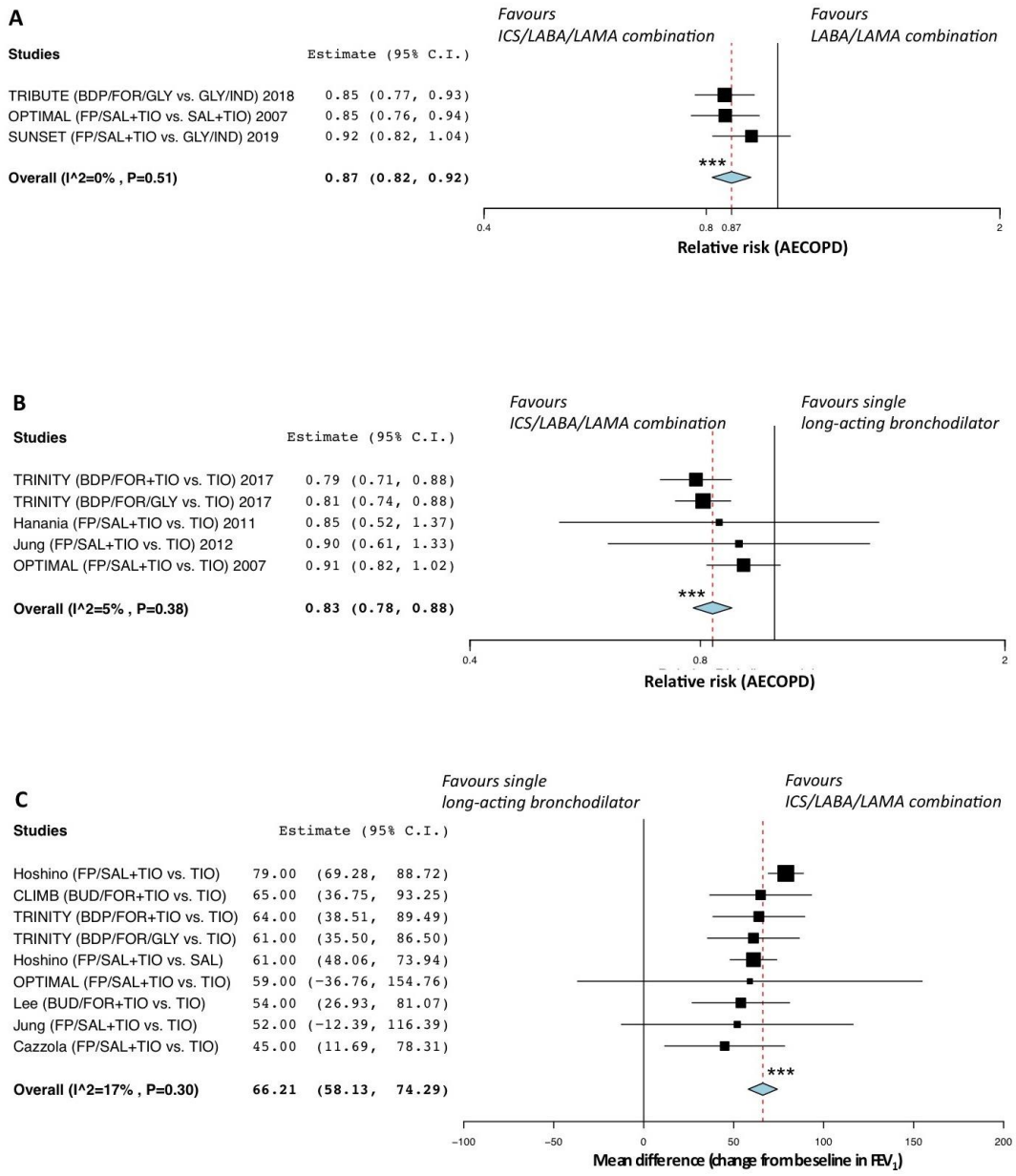

Figure S4. Sensitivity analysis for the impact of ICS/LABA/LAMA combination vs. LABA/LAMA combination (A) and single long-acting bronchodilator therapy (B) on the risk of severe AECOPD, and for the ICS/LABA/LAMA combination vs. single long-acting bronchodilator therapy on the change from baseline in FEV_1 (C). The studies have been sorted by the extent of effect. ***P<0.001 vs comparators. AECOPD: acute exacerbation of COPD; BDP: beclometasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic receptor antagonist; SAL: salmeterol; TIO: tiotropium bromide.

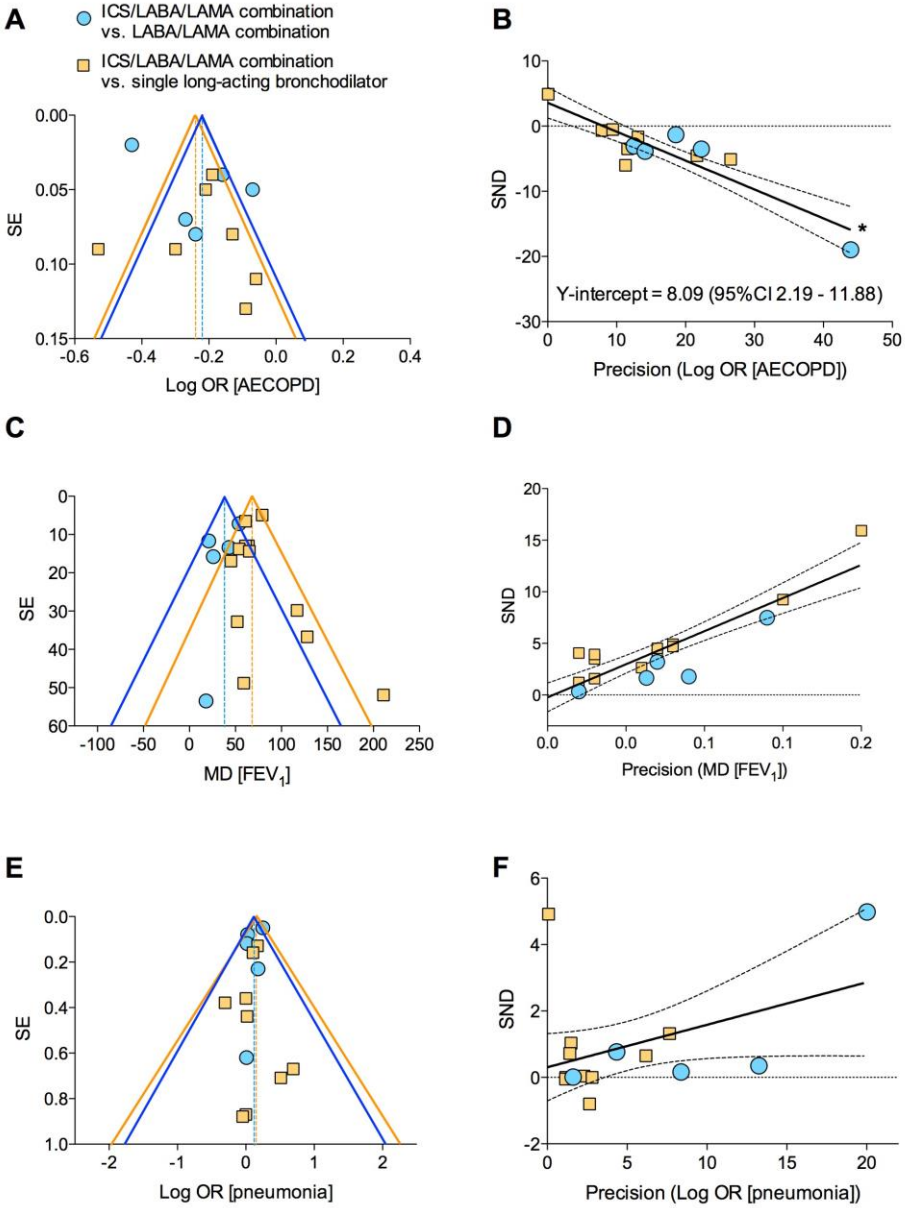

Figure S5. Funnel plots (left panels) and graphical representations of Egger's test (right panels) for the impact of ICS/LABA/LAMA combination vs. LABA/LAMA combination and single long-acting bronchodilator therapy on the risk of moderate or severe AECOPD (A and B), change from baseline in FEV_1 (C and D), and risk of pneumonia (E and F) in COPD patients. Funnel plot represents a visual approach to check for the existence of publication bias by assessing the symmetry of study distribution, whereas Egger's test is a regression assay that permits to statistically quantify the extent of Funnel plot asymmetry. * Y-intercept significantly (P<0.1) different from zero. AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic receptor antagonist; MD: mean difference; OR: odds ratio; SE: standard error; SND: standard normal deviate.

References

1. Calzetta L, Rogliani P, Ora J*, et al.* LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment. DOI: 10.1183/16000617.0043-2016. *Eur Respir Rev* 2016; 0: 1-11.

2. Dobler CC, Wilson ME, Murad MH. A pulmonologist's guide to understanding network meta-analysis. *Eur Respir J* 2018; 52

3. Cazzola M, Calzetta L, Rogliani P*, et al.* Tiotropium formulations and safety: a network meta-analysis. Doi: 10.1177/2042098616667304. *Therapeutic Advances in Drug Safety* 2016: 2042098616667304.

4. Calzetta L, Rogliani P, Matera MG*, et al.* A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD. *Chest* 2016; 149: 1181-1196.

5. Cazzola M, Rogliani P, Calzetta L*, et al.* Impact of Mucolytic Agents on COPD Exacerbations: A Pair-wise and Network Meta-analysis. *COPD* 2017; 14: 552-563.

6. Cazzola M, Calzetta L, Barnes PJ*, et al.* Efficacy and safety profile of xanthines in COPD: a network meta-analysis. *Eur Respir Rev* 2018; 27

7. Aaron SD, Fergusson DA. Exaggeration of treatment benefits using the “event-based” number needed to treat. *Can Med Assoc J* 2008; 179: 669-671.

8. Cazzola M, MacNee W, Martinez FJ*, et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416-469.

9. Jones PW, Beeh KM, Chapman KR*, et al.* Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med* 2014; 189: 250-255.

10. Vestbo J, Papi A, Corradi M*, et al.* Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017

11. Papi A, Vestbo J, Fabbri L*, et al.* Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076-1084.

12. Lipson DA, Barnhart F, Brealey N*, et al.* Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. DOI: 10.1056/NEJMoa1713901. *N Engl J Med* 2018

13. Moher D, Shamseer L, Clarke M*, et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015; 4: 1.

14. Chapman KR, Hurst JR, Frent SM*, et al.* Long-term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in COPD Patients (SUNSET): a Randomized, Double-Blind, Triple-Dummy Clinical Trial. *Am J Respir Crit Care Med* 2018

15. Lee SD, Xie CM, Yunus F*, et al.* Efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with severe or very severe COPD: A randomized, multicentre study in East Asia. *Respirology* 2016; 21: 119-127.

16. Saito T, Takeda A, Hashimoto K*, et al.* Triple therapy with salmeterol/fluticasone propionate 50/250 plus tiotropium bromide improve lung function versus individual treatments in moderate-to-severe Japanese COPD patients: a randomized controlled trial - Evaluation of Airway sGaw after treatment with tripLE. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 2393-2404.

17. Magnussen H, Disse B, Rodriguez-Roisin R*, et al.* Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014; 371: 1285-1294.

18. Hoshino M, Ohtawa J. Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. *Respiration* 2013; 86: 280-287.

19. Jung KS, Park HY, Park SY*, et al.* Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med* 2012; 106: 382-389.

20. Hanania NA, Crater GD, Morris AN*, et al.* Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med* 2012; 106: 91-101.

21. Welte T, Miravitlles M, Hernandez P*, et al.* Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 180: 741-750.

22. Singh D, Brooks J, Hagan G*, et al.* Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 2008; 63: 592-598.

23. Cazzola M, Ando F, Santus P*, et al.* A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulm Pharmacol Ther* 2007; 20: 556-561.

24. Aaron SD, Vandemheen KL, Fergusson D*, et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; 146: 545-555.